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Note

Synthesis of Novel Heterocycles Through Reaction of Indolin-2-one Derivatives with Active Methylene and Amino Reagents

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Several new spiro compounds were synthesized via one-pot ternary condensation of isatin, malononitrile and each of thiobarbituric acid, barbituric acid, 3-methyl-pyrazolin-5-one, 1-phenyl-3-methyl-pyrazolin-5-one, acetylacetone, benzoylacetone, ethyl acetoacetate, phenacyl cyanide or ethyl-cyanoacetate dimer. Structures and reaction mechanisms were reported and supported via a second synthetic route.

Key words : Heterocycles, Indolin-2-one, Malononitrile, Methylene and amino reagents

INTRODUCTION

Isatin is one of the most interesting molecules which show a wide spectrum of chemical and biological activities (Tomchin, 1990; Yamagishi *et al.*, 1990; Lacassagne *et al.*, 1955; Bigot *et al.*, 1972; Eistert and Selzer, 1962). This work is a part of our programme for the synthesis of heterocyclic compounds of applied value from isatin and its derivatives (Mohamed *et al.*, 1985; Fahmy *et al.*, 1984; Abdel-Latif, 1990; Abdel-Latif *et al.*, 1994).

METERIALS AND METHODS

Melting points (°C) were obtained on a Gallenkamp melting point appratus (open capillary tubes) and were uncorrected. ^{1}H-NMR spectra were performed on a Varian EM-390 (90 MHz) spectrometer with TMs as an internal standard and with chemical shifts expressed in δ (ppm) values. IR spectra were recorded on a Shimadzu-470 spectrophotometer (KBr pellet). Elemental analysis (C, H, N) of compounds **9**, **10** and **18-24** were in agreement with the proposed structures. The synthetic and spectral data of the new derivatives are reported in Table I and II, respectively.

Synthesis of 9, 10 and 18-24

Method A: An equimolar (0.01 mol) mixture of isatin **1**, malononitrile **2** and the compounds **3**, **4** and **11-17**, respectively, in ethanol (50 ml) was treated with piperidine (0.1 ml), the reaction mixture was refluxed for 1-3 h, during which the respective product was separated out or after cooling, it was separated out by trituration with cold water. The product was filtered off, dried in air and crystallized from an appropriate solvent (Table I).

Method B: An equimolar (0.01 mol) mixture of **5** and the compounds **3, 4, 11-17** respectively, in ethanol (50 ml) was treated with piperidine (0.1 ml). The reaction mixture was refluxed for 2-4 h and worked up as described in method A to afford the respec-

Table I. Synthetic data for compounds **9, 10, 18-24**

Comp. No. (Col.)	Yield (%)	Cryst. Solv.	mp. °C	Molecular Formula (M. Wt.)
9	80	EtOH/DMF	225~227	$C_{15}H_9N_5O_4$
(buff)			225~256	323.26
10	85	EtOH/DMF		$C_{15}H_9N_5O_3S$
(buff)			273	339.33
18	88	EtOH		$C_{15}H_{11}N_5O_2$
(Colourless)			222~225	293.28
19	80	EtOH		$C_{21}H_{15}N_5O_2$
(Colourless)			248~249	369.37
20	82	EtOH		$C_{16}H_{13}N_3O_3$
(buff)			250~252	295.28
21	70	EtOH		$C_{21}H_{15}N_3O_3$
(buff)			258~260	357.35
22	75	EtOH		$C_{17}H_{15}N_3O_4$
(Colourless)			225~226	325.31
23	70	EtOH		$C_{20}H_{12}N_4O_2$
(Colurless)			284~285	340.33
24	88	EtOH		$C_{21}H_{19}N_5O_5$
(Yellow)				421.39

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Table II. IR and [1]H-NMR data of compounds **9, 10, 18-24**

Comp.	IR (cm^{-1} selected bands)	[1]H-NMR; δ ppm
9	3400-3180 (OH, NH_2, NH); 2200 (CN), 1720 (CO)	4.4-4.7 (m, 4H, NH_2+2OH); 6.8-8.1 (m, 4H, 4Ar-H); 110.0 (s, 1H, NH)
10	3300-3180 (OH, NH_2, NH); 2200 (CH); 1710 (CO)	4.5 (br, m, 4H, NH_2+SH+OH); 6.0-8.1 (m, 4H, 4Ar, H); 10.8 (s, 1H, NH)
18	3400-3200 (NH_2, NH); 2200 (CN); 1720 (CO)	1.6 (s, 3H, CH_3); 6.8-7.4 (m, 6H, 4Ar-H+NH_2); 11.2 (s, 1H, NH); 11.5 (s, 1H, NH)
19	3450, 3300, 3200 (NH_2, NH); 2200 (CN); 1690 (CO)	1.6 (s, 3H, CH_3); 6.8-7.8 (m, 11H, 9Ar-H+NH_2); 11.0 (s, 1H, NH)
20	3300, 3150 (NH_2, NH); 2200 (CN); 1710 (CO, ring); 1670 (CO)	1.5 (s, 3H, CH_3); 2.4 (s, 3H, CH_3, acetyl); 6.5-7.8 (m, 6H, 4Ar-H+NH_2); 11.2 (s, 1H, NH)
21	3450, 3300, 3150 (NH_2, NH); 2200 (CN), 1720 (CO ring); 1670 (CO)	1.6 (2, 3H, CH_3); 6.7-8.3 (m, 11H, 9Ar-H+NH_2); 11.2 (s, 1H, NH)
22	3450, 3300, 3150 (NH_2, NH); 2200 (CN); 1735 (CO, ester); 1710 (CO, ring)	0.8 (t, 3H, CH_3, ester); 1.7 (s, 3H, CH_3); 3.7 (q, 2H, CH_2); 7.0-8.1 (m, 6H. 4Ar-H+NH_2); 10.9 (s, 1H, NH)
23	3300-3150 (NH_2, NH); 2200 (CN); 1720 (CO)	6.9-8.3 (m, 11H, 9Ar-H+NH_2); 10.9 (s, 1H, NH)
24	3400, 3300, 3200 (NH_2, NH); 2230 (CN); 2200 (CN); 1740-1730 (CO, ester); 1720 (CO)	1.2 (t, 3H, CH_3); 1.5 (t, 3H, CH_3); 2.0 (s, 1H, NH, pyrid.); 3.7 (s, 1H, CH); 4. 0-4.4 (overlapped qq, 4H, $2CH_2$); 6.9-7.5 (m, 6H, 4Ar-H+NH_2), 10.8 (s, 1H, NH)

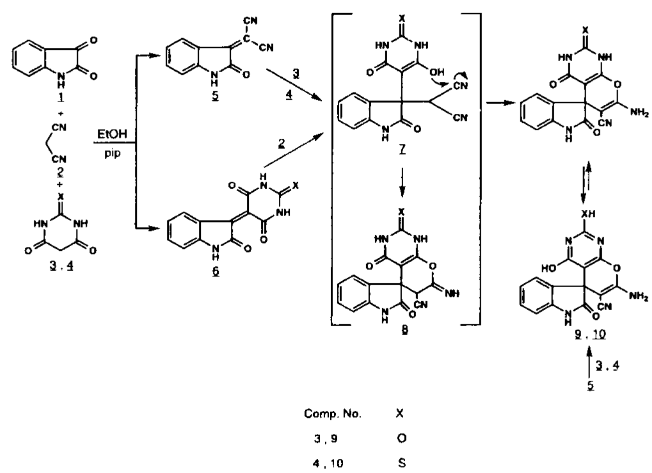
tive product (mp., mixed mp.) (Table I).

RESULTS AND DISCUSSION

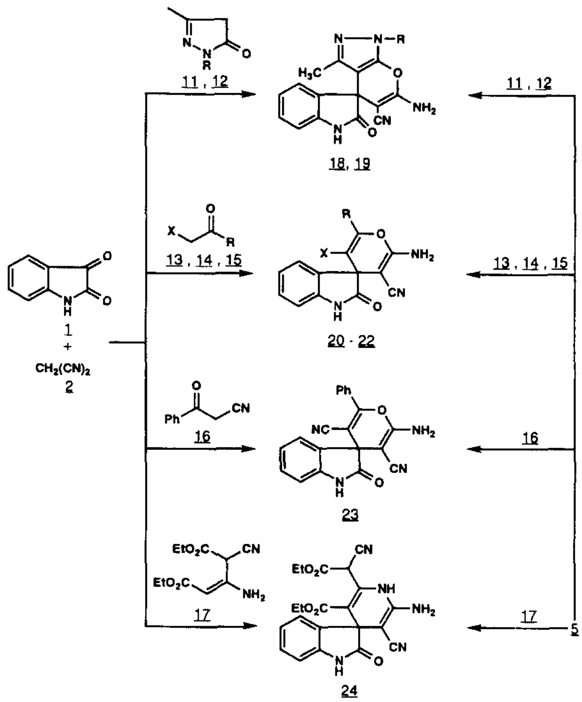
In this communication we found that refluxing a ternary mixture of isatin **1**, malononitrile **2** and barbityric acid **3** (or thiobarbituric acid **4**) in a molar ratio of 1:1:1 in ethanolic piperidine solution afforded compound **9** (or **10**) has been supported by analytical and spectral data. The IR spectra of **9** and **10** showed NH_2, NH and Cn bands in the rang of 3400-3180 cm^{-1} and at 2200 cm^{-1}, respectively. The [1]H-NMR spectra of **9** (and **10**) showed the NH_2 OH (and SH) protons in a broad multiplet at δ 4.4~4.7 (and at δ 4.5); the aromatic protons in a multiplet at δ 6.8~8.1 (and at δ 6.9~8.1) and the NH singlet at δ 11.0 (and at δ 10.8), respectively (Table II). The reaction mechanism was assumed to proceed as depicted in Scheme I. The initial condensation of isatin **1** with malononitrile **2** to afford the yliden 3-(dicyanomethylidene) indolidin-2-one **5** followed by the addition of the active methylene group in barbituric acid **3** (or thiobarbituric acid **4**) to the ylidenic bond in **5** forming an acyclic intermediate 7. Compound 7 underwent intramolecular cycloaddition of an enol OH to a cyano forming the intermediat **8** that tautomerized to form the final isolated product **9** (or **10**) (Scheme **1**).

Compounds **9** and **10** were assigned, respectively, as 7'-amino-6'-cyano-2',4'-dihydroxyspiro[indoline-3,5'-(1H)-pyrano(2,3-d)pyrimidinel-2-one and 7'-amino-6'-cyano-4'-hydroxy-2'-mercapto-spiro[indoline-3,5'(1H)-pyrano(2,3-d)-pyrimidine]-2'-one. The structures of **9** and **10** were further confirmed through an unambiguous synthesis by the reaction of **5** with **3** or **4** respectively, under the same reaction conditions (mp., mixed mp.) (Scheme 1).

The ternary condensations of isatin **1**, malononitrile **2** and different uncleophiles **11-17** were also examined (Scheme 2). Thus, with 3-methyl-pyrazolin-5-one **11** it give spiro[indoline-3,4'(1H)-pyrano[2,3-dpyrazole] 2-one derivative **18**, whereas with 1-phenyl-3-methyl-pyrazolin-5-one **12** it afforded spiro[indoline-3,4'(1H)-pyrano[2,3-c]-pyrazole]-2-one derivative **19**, while with acetylacetone **13**, benzoylacetone **14**, ethyl acetoacetate **15** and phenacyl cyanide **16** the corresponding spiropyran-4-yl-indolidene derivatives **20-22** and **23** were obtained, respectively. Using ethylcyanoacetate dimer **17** as a nucleophile afforded the spiro pyridine-4-yl-indolidene derivative **24**. The structures of **18-24** were established on the basis of elemental, IR and [1]-



Scheme 1.



Comp. No.	R	X
18	H	
19	Ph	
20	CH_3	$COCH_3$
21	CH_3	COPh
22	CH_3	CO_2Et

Scheme 2.

NMR spectral (Table II) analyses. Moreover, compounds **18-24** were unambiguously synthesized via reacting the ylidene **5** with each of compounds **11-17**, respectively, (mp., mixed mp.) (Scheme 2). The reaction mechanism for the formation of **18-24** was assumed to be in the same line as that suggested for **9** and **10**.

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